Controlled Release KCl Tablet Formulations

Background of the Invention

There is a high incidence of severe potassium deficiency in patients treated simultaneously with diuretics and carbenoxolone. In order to maintain the extracellular and intracellular concentrations of potassium within relatively narrow limits, large doses of potassium are required. These doses are released in the body in a controlled release fashion in order to avoid achieving life-threatening toxicity. The strengths of the most dosage forms available in the market place are 8 and 10 mEq KCl capsules or tablets. Since a 20 mEq KCl capsule formulation (exceeding 2 g in weight) is not feasible, there is a need for a 20 mEq KCl tablet formulation. There is a 20 mEq KCl tablet that is commercially available under the tradename, K-DUR 20, based on KCl granules coated with a coating composition comprising of ethyl cellulose (Ethocel Standard Premium 100 or Ethocel Medium 100 from Dow Chemical) and hydroxypropyl cellulose (Klucel from Hercules) using a fluid bed granulator which is made under U.S. Patent 4,863,743 issued to C. Hsiao and T. Chou of Key Pharmaceuticals, Inc.

Summary of the Invention

An object of the present invention is to provide a method for manufacturing pharmaceutically elegant KCl tablets having sustained release properties (e.g., releasing not more than 40% in one hr and not less than 80% over 8 hrs when tested in USP Apparatus 2 (Paddles @ 50 rpm) in purified water. Another object is to provide tablets with controlled release characteristics, thereby providing treatments for potassium deficiency in humans while minimizing adverse side effects if possible. Since 20 mEq active is equivalent to almost 1500 mg Kcl, it is difficult to provide this dosage in a single tablet, which can deliver an effective daily dose of potassium without being unduly large for swallowing. A more particular but non-limiting further objective of the invention is to provide tablets of total tablet weight of about 2 g (preferably under 2 g) with acceptable hardness (not less than 10 kP) and friability (not more than 1.5%).

US Patent 5,422,122 teaches the art of making a pharmaceutical dosage form by first forming KCl microcapsules by coacervation in a cyclohexane solution of ethylcellulose, overcoating the microcapsules with hydroxypropylcellulose and compressing the resulting microcapsules into 20 mEq KCl tablets. This patent is incorporated here in its entirety. Microencapsulated KCl granules produced by solvent coacervation of ethylcellulose are often glassy hard granules with poor compactibility characteristics. In order to improve the compressibility/compactibility of the microcapsules, film coating with a variety of plasticized, pharmaceutically acceptable polymeric materials was attempted. Polymeric materials found suitable for improving ethylcellulose coated KCl microcapsules include acacia, alginic acid or its salt, corn starch, gelatin, xanthan gum, polyvinylpyrrolidone (PVP), sodium carboxymethylcellulose, methylcellulose, low molecular weight ethylcellulose (EC) and hydroxypropylmethyl cellulose (HPMC) alone or in combination. Different plasticizers such as triacetin, triethyl citrate, dibutyl sebacate, polyethylene glycol of molecular weight ranging from 200 to 8,000, were evaluated alone or in combination. These attempts have resulted in pharmaceutically elegant 20mEq KCl capsule-shaped tablets weighing about 2 g (generally less) and having controlled release properties (releasing not more than 40% in one hr and not less than 80% over 8 hrs) when tested in USP Apparatus 2 (Paddles @ 50 rpm) in purified water.

Thus, one manifestation of the present invention is an improved 20 mEq KCl controlled release dosage form prepared from a multiplicity of ethylcellulose microencapsulated potassium chloride crystals, which are further coated with a plasticized water swellable/soluble polymer or a blend. These membrane coated granules are capable of being compressed into pharmaceutically elegant, easily swallowable 20 mEq KCl tablets of acceptable hardness and friability. Of course other KCl dosages are also within the scope of the invention. Another manifestation of the present invention is a method for preparing microencapsulated KCl crystals and a method for preparing a KCL tablet.

Detailed Description of the Invention

A plurality of potassium chloride crystals, preferably from about 20 mesh to about 70 mesh, more preferably from about 30 mesh to about 50 mesh, are coated with two distinct

layers. The first layer applied to the crystals is composed of ethylcellulose. Utilization of a high viscosity ethylcellulose such as one with a viscosity of from about 90 to about 110 cp, e.g., Ethocel 100 (Dow Chemical Corp.) allows the crystals to retain their diffusion controlling characteristics even after compression into a tablet form. The ethylcellulose may be applied by any suitable technique known in the art, but is preferably applied by coacervation using polyethylene as a phase separator as described in U. S. Patent 5,422,122. If coacervation is used, trace amounts of the phase separator may be present in the first layer, preferably in an amount less than about one percent by weight of the ethylcellulose coated crystals.

The ethylcellulose layer is preferably applied to the KCl crystals in an amount of about 8 to about 20 percent, more preferably from about 11 to about 15 percent, of the total weight of the uncoated potassium chloride crystals. This first layer controls the release of the potassium chloride over time, total release time being proportionally dependent upon the thickness of ethylcellulose. After application of the ethylcellulose, a drying step should preferably be carried out for such a time period and at such temperatures so that the microencapsulated crystals do not adhere to one another. The resultant ethylcellulose encapsulated potassium chloride microcapsules are preferably of such a size that less than 5% are greater than 20 mesh.

A second, discrete layer of at least one hydrophilic (water swellable/soluble) polymer coating, is applied over the first layer of ethylcellulose. Hydrophilic polymer coatings include, but are not necessarily limited to acacia, alginic acid or its salt, corn starch, gelatin, xanthan gum, polyvinylpyrrolidone (PVP), sodium carboxymethylcellulose, methylcellulose, low molecular weight ethylcellulose (Ethocel with a viscosity from about 4 to 20 cps) and hydroxypropylmethyl cellulose (HPMC) such as Methocel E5 or 15. These hydrophilic polymers can be used alone or in combination.

In accordance with the invention the hydrophilic polymer layer is plasticized. Suitable plasticizers include triacetin, triethyl citrate, dibutyl sebacate (DBS), polyethylene glycol (PEG) of molecular weight ranging from 200 to 8,000 (e.g., a blend of PEG 400 and PEG 4000). The plasticizers can be used alone or in combination. The plasticizer is typically used in an amount of about 2 to 30% based on the combined weight of the hydrophillic polymer and plasticizer. The amount will vary with the type of plasticizer and the nature of the hydrophillic

polymer. For example for HPMC and PEG400 the ratio can vary from about 70/30 to 90/10. With PVP, DBS or triethyl citrate can be used as the plasticizer in a ratio of 94/6 to 97/3.

The plasticized hydrophilic layer is applied by conventional techniques, such as from an aqueous solution using a fluidized bed coater, to the preformed layer of ethylcellulose. The hydrophilic polymer coating layer inclusive of the plasticizer is applied in an amount of about 0.5 to 5% w/w (preferably about 1 to 3% w/w and still more typically 2% w/w) of the weight of the ethylcellulose coated crystals.

The hydrophilic polymer does not significantly diffuse into the ethylcellulose, but rather forms a distinct second layer. The first membrane of ethylcellulose coacervated in the absence of any plasticizer can be easily distinguishable from the plasticized polymeric membrane by microscopic/spectroscopic techniques. As this layer is soluble to gastric fluids, the hydrophilic polymer coating dissolves following ingestion of the resultant tablet. For all practical purposes, it does not contribute to the controlled release of potassium chloride. Rather, the hydrophilic polymer coating is present primarily as a binder material so that a high dosage rate tablet can be formed with a minimal amount of conventional excipients and low compaction pressures to allow minimal disruption of the rate controlling ethylcellulose membrane. In addition, this formulation allows the microencapsulated potassium chloride to be dispersed essentially intact over a wide area, reducing the risk of gastric irritation.

After the hydrophilic polymer coating layer is applied, the now twice coated crystals are subjected to a final drying step. The resultant coated potassium chloride microcapsules are preferably of such a size that less than 15%, are greater than 20 mesh. The coated crystals may then be formed into tablets by compression using conventional techniques. Preferably a minimal amount of excipients, no more than about 15% more preferably no more than 12%, and most preferably no more than 7% by weight based on the weight of the final dosage tablet, is added to the coated crystals prior to compression. The term "excipients," as used herein, refers to any additional pharmaceutically acceptable ingredients which may be used in a tablet. These excipients include, but are not limited to, ingredients such as diluents or binders, disintegrants, wetting agents, and lubricating agents. Representative binders include, but are not limited to, Klucel Registered LF (hydroxypropylcellulose) and Avicel Registered

(microcrystalline cellulose). Disintegrants include, but are not limited to, cornstarch, lactose, mannitol, sucrose, Avicel Registered (microcrystalline cellulose), Primogel Registered (sodium carboxymethyl starch, Emcompress Registered (dibasic calcium phosphate dihydrate), Crospovidone Registered (cross linked polyvinyl pyrrolidone), and tricalcium phosphate. Wetting agents include, but are not limited to sodium lauryl sulfate. Lubricating agents include, but are not limited to stearates (e.g. magnesium, calcium, and sodium), stearic acid, Sterotex Registered, talc, waxes, and Stearowet Registered.

In a particular embodiment of the invention, the ethylcellulose KCl microcapsules coated with a plasticized polymer coating solution are blended with a diluent, preferably microcrystalline cellulose, optionally a disintegrant and/or a lubricant, and compressed into capsule shaped tablets. In one embodiment, a disintegrant such as crosslinked PVP (Crospovidone) or sodium starch glycolate at a level of 0.2 to 2% w/w and/or a lubricant/surfactant such as sodium lauryl sulfate is optionally blended with the compression mix. In the course of these investigations, it was discovered that sodium lauryl sulfate, widely used as a surfactant produce strong tablets with low friability. It was also discovered that microcapsules fluid bed coated with the plasticized polymeric systems discussed in this patent application could be compressed into strong tablets with low friability without a lubricant (magnesium stearate) or a surfactant (sodium lauryl sulfate).

The final tablets will contain a pharmaceutically acceptable amount of potassium chloride. Acceptable daily dosages may be found in The Physicians' Desk Reference, 45th ed. (1991), e.g., 20-200 mEq/day thereof, preferably from about 8 mEq to about 20 mEq. The pharmaceutically elegant 20 mEq Microcaps KCl tablets will exhibit sustained release properties (releasing not more than 40% in one hr and not less than 80% over 8 hrs when tested in USP Apparatus 2 (Paddles @ 50 rpm) in purified water, thereby providing treatments for potassium deficiency in humans with minimal adverse side effects.

Typical formulations are given in Example 1-3. Unless otherwise indicated all parts are by weight.

Ingredients	Example 1	Example 2	Example 3
Film Coating			
Microcaps KCl	1714.3	1714.3	1714.3
HPMC E5	6.2	30.8	31.5
PEG 400	2.6	13.2	
1/1PEG 400/PEG 4000			3.5
Compression Mix			
Film coated KCl	1723.1	1758.3	1749.3
Microcryst. Cellulose	186.2	200.9	174.9
Crosslinked PVP	39.2	19.9	
Sod. Lauryl sulfate	9.8	9.9	
Total Tablet weight	**1960.2**	**1989.0**	**1943.2**

Example 1

Microcaps KCl granules (KCl crystals microencapsulated in ethylcellulose) with a 87.5 KCl content were coated with an aqueous solution of hydroxypropylmethyl cellulose (HPMC) and polyethylene glycol 400 (PEG 400) at a ratio of 77/23 to achieve a weight gain of 0.5% w/w. The film coated granules were blended with microcrystalline cellulose (MCC), crosslinked PVP and sodium lauryl sulfate in an amounts of at 9.5%, 2.0% and 0.5% w/w, respectively and compressed into tablets weighing 1960 mg on a rotary tablet press. These tablets containing 1500 mg of Microcaps KCl release slowly over a period of 10 hrs when dissolved in 0.1N HCl using USP Apparatus 2.

Example 2

Microcaps KCl granules (KCl crystals microencapsulated in ethylcellulose) with a

87.5 KCl content were coated to achieve a weight gain of 2.5% w/w with an aqueous solution of HPMC and PEG 400 at a ratio of 77/23. The film coated granules were blended with microcrystalline cellulose and crosslinked PVP at 10.0 and 1.0% w/w, respectively and compressed into tablets weighing 1989 mg on a rotary tablet press. These tablets containing 1500 mg active as Microcaps KCl release slowly over a period of 10 hrs when dissoluted in 0.1N HCL using USP Apparatus 2.

Example 3

Microcaps KCl granules (KCl crystals microencapsulated in ethylcellulose) with a 87.5 KCl content were coated with an aqueous solution of HPMC and PEG 400 at a ratio of 77/23 to achieve a weight gain of 1.0% w/w. The film coated granules were blended with microcrystalline cellulose, crosslinked PVP and magnesium stearate at 9.5%, 2.0 and 0.5% w/w, respectively and compressed into tablets weighing 1968 mg on a rotary tablet press. These pharmaceutically elegant tablets containing 1500 mg active as Microcaps KCl release slowly over a period of 10 hrs when dissoluted in 0.1N HCl using USP Apparatus 2.

Ingredients	Example 4	Example 5	Example 6
Film Coating			
Microcaps KCl	1714.3	1714.3	1714.3
PVP (K-30)	31.5	31.5	
1/1Ethocel/PVP			31.5
1/1 PEG 400/PEG 4000	3.5		
Tri-ethyl citrate		3.5	
Dibutyl sebacate			3.5

Compression Mix

Film coated KCl	1749.3	1749.3	1749.3
Microcryst. Cellulose	194.4	196.6	194.3
Crosslinked PVP		19.6	
Total Tablet weight	**1943.7**	**1965.5**	**1943.7**

Example 4

Microcaps KCl granules (KCl crystals microencapsulated in ethylcellulose) with a 87.5 KCl content were coated with an aqueous solution of polyvinylpyrrolidone (PVP K-30) containing 1:1 PEG 400/PEG 4000 at 10% w/w to achieve a weight gain of 2.0% w/w. The film coated granules were blended with microcrystalline cellulose at 10.0% w/w and compressed into tablets weighing 1944 mg on a rotary tablet press. These tablets containing 1500 mg active as Microcaps KCl release slowly over a period of 10 hrs when dissoluted in 0.1N HCl using USP Apparatus 2.

Example 5

Microcaps KCl granules (KCl crystals microencapsulated in ethylcellulose) with a 87.5 KCl content were coated to achieve a weight gain of 2.0% w/w with an aqueous solution of PVP and tri-ethyl citrate at a ratio of 97/03. The film coated granules were blended with microcrystalline cellulose and crosslinked PVP at 10.0 and 1.0% w/w, respectively and compressed into tablets weighing 1965 mg on a rotary tablet press. These tablets containing 1500 mg active as Microcaps KCl release slowly over a period of 10 hrs when dissoluted in 0.1N HCl using USP Apparatus 2.

Example 6

Microcaps KCl granules (KCl crystals microencapsulated in ethylcellulose) with a 87.5 KCl content were coated with an IPA/acetone solution of PVP/Ethocel/DBS at a ratio of 48/48/04 to achieve a weight gain of about 2.0% w/w. The film coated granules were blended with microcrystalline cellulose at 10% w/w and compressed into tablets weighing 1944 mg on a rotary tablet press. These pharmaceutically elegant tablets containing 1500 mg active as Microcaps KCl release slowly over a period of 10 hrs when dissoluted in 0.1N HCl using USP Apparatus 2.

The above examples are provided to show how to practice the present invention and are not intended to be exhaustive or to include all obvious modifications and variations which will become apparent to those skilled in formulation development. However, all these modifications are within the scope of the present invention and by the following claims:

What is claimed is: